PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 12

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
29312-0106		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/01112	25/09/2000	24/09/1999
International Patent Classification (IPC) or national classification and IPC A61K35/00		
Applicant VASOGEN IRELAND LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☒	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/04/2001	18.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schnack, A Telephone No. +49 89 2399 8149

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/01112

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-23	as originally filed				

Claims, No.:

1-16	as received on	12/11/2001	with letter of	12/11/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 14-16.

because:

   ☒ the said international application, or the said claims Nos. 14-16 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide

and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	none
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations
see separate sheet

Reference is made to the following documents:

D1: WO 96 346 13
D2: WO 00 290 03
D3: WO 99 138 90
D4: WO 98 074 36
D5: Martindale, The Extra Pharmacopoeia, 32th Ed.

Section I
Basis

The amendment to claim 2 (**0.2** - 100 ml) does not appear to be acceptable, because it appear that the originally filed disclosure describes solely **0.1** - 100 ml, (Rule 70.2(c) PCT).

Section II
Priority

The presently claimed priority right has been checked and found valid. D2 does not appear to anticipate the novelty of the present subject matter, for which reason D2 must be disregarded in the assessment of patentability of the present subject matter.

Section III
Non-establishment of opinion

Claims 14-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V
V.1. Novelty
Remarks under Article 33(2) PCT:

The present treatment of autologous blood is known from D1, D3 and D4, (see the claims).

However, D1 uses said ex-vivo treated blood for treating patients suffering from a vasospastic disorder and D1 does not disclose concurrent treatment with a cholesterol lowering drug.

D3 discloses the presently ex-vivo treated blood for treating symptoms of stress such as elevated blood pressure. D3 does not explicitly disclose treatment of patients, which receive treatment with cholesterol lowering drugs.

D4 discloses the presently ex-vivo treated blood for treating an autoimmune disease, such as rheumatoid arthritis. No disclosure of treatment of patients, which concurrently receive cholesterol lowering drugs appears to be present in D4.

Thus, the present subject matter appears to be novel with respect to the cited references.

V.2. Inventive step

Remarks under Article 33(3) PCT:

The present subject matter is based on the alleged synergistic effect on atherosclerosis of a combination treatment comprising a "cholesterol lowering drug" and the ex-vivo treated blood according to D1, D3 and D4. However, no data supporting this allegation appears to be presented in the present application, for which reason the present synergistic effect must presently be considered to be speculative.

Moreover, D1 teaches administration of the present ex-vivo treated blood to patients suffering from inter alia atherosclerosis, (see D1, page 2, lines 8-15 and claim 10). Thus, starting from D1, the objective technical problem to be solved can be formulated as the provision of an improved treatment of atherosclerosis. Since it is known that atherosclerosis is at least partly caused by excessive quantities of cholesterol deposits on the endothelium of the blood vessels, (cf. present page 1, lines 15-25), it appears that the skilled man would combine two treatments, (the ex-vivo treated blood according to D1 and the known cholesterol lowering drugs, e.g. statins according to

D5), with a reasonable expectation of an improved outcome of said combined treatment. Thus, the presently claimed treatment does not appear to be more that a simple combination treatment of a specific condition, (atherosclerosis caused by hyper cholesterolemia), said combined treatment utilising two known effective treatments. Such a combination does not appear to involve an inventive step.

V.3. Industrial applicability

Remarks under Article 33(4) PCT:

For the assessment of the present claims 14-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

WHAT IS CLAIMED IS:

1. Use in preparation of a medicament for administration to a patient undergoing treatment with a cholesterol lowering drug, to alleviate atherosclerosis in the patient and/or reduce serum lipid levels in the patient, of an aliquot of the patient's blood which has been treated ex vivo with one or more stressors selected from an oxidative environment, thermal stress and UV light.

2. Use as claimed in Claim 1 wherein the patient is undergoing treatment with a statin cholesterol lowering drug.

3. Use according to claim 2 wherein the statin drug is selected from atorvastatin, pravastatin, lovastatin, fluvastatin, simvastatin and cerivastatin.

4. Use as claimed in any preceding claim wherein the aliquot of the patient's blood has a volume of from 0.1 - 100 ml.

5. Use as claimed in any preceding claim wherein the blood aliquot has bee ex vivo treated with an oxidative environment and UV light, optionally also with thermal stress.

6. Use as claimed in claim 5 wherein the oxidative stressor is a chemical oxidizing agent, applied to the blood aliquot simultaneously with the application of the UV light stressor.

7. Use as claimed in claim 6 wherein the chemical oxidizing agent is a gaseous mixture of ozone and oxygen, applied by bubbling through the blood aliquot while the aliquot is subject to incident UV light stressor.

8. Use according to claim 7 wherein a thermal stressor, in the form of a temperature above or below normal body temperature, is applied to the blood aliquot simultaneously with the application of the ozone/oxygen gas mixture and the UV light.

9. Use as claimed in any preceding claim wherein the UV light

stressor is UV light in the UV-C band wavelength.

10. Use as claimed in any preceding claim wherein the stressors are applied ex vivo to the blood aliquot for a period of from about 2 - 5 minutes.

11. Use according to any preceding claim wherein the patient's cholesterol lowering drug treatment is administration of atorvastatin, at a daily dosage of 5 - 200 mg.

12. Use according to any preceding claim wherein the patient's cholesterol lowering drug treatment is administration of pravastatin, at a daily dosage of 5 - 200 mg.

13. Use according to any preceding claim wherein the patient's cholesterol lowering drug treatment is administration of simvavastatin, at a daily dosage of 5 - 200 mg.

14. Use according to any preceding claim wherein the patient's cholesterol lowering drug treatment is administration of fluvastatin, at a daily dosage of 5 - 200 mg.

15. Use according to any preceding claim wherein the patient's cholesterol lowering drug treatment is administration of lovastatin, at a daily dosage of 5 - 200 mg.

16. Use according to any preceding claim wherein the patient's cholesterol lowering drug treatment is administration of cerivastatin, at a daily dosage of 0.1 - 0.8 mg.

17. A combination treatment for slowing or arresting the progression and/or effecting the regression of atherosclerotic plaque deposits and/or improving the stability of such plaques in a mammalian patient, said combination treatment including the administration to the patient of a cholesterol lowering drug and the administration to the patient of an aliquot of a patient's own blood which has been treated ex vivo with one or more stressors selected from an oxidative environment, thermal stress and UV

light.

18. The use of an aliquot of a patient's own blood which has been treated ex vivo with one or more stressors selected from an oxidative environment, thermal stress and UV light; and a cholesterol-lowering drug, for reducing serum lipid levels and/or combating development of atherosclerosis in a mammalian patient.

19. A process for enhancing the reduction in serum lipid levels in a mammalian patient caused by administration of a cholesterol-lowering drug, which comprises administering to the patient an aliquot of the patient's own blood which has been treated ex vivo with one or more stressors selected from an oxidative environment, thermal stress and UV light and administering to a patient a cholesterol-lowering drug.

20. The invention as claimed in any of claims 17, 18 or 19 wherein the cholesterol-lowering drug is a statin drug.